Original Article

Early Recurrence of Pancreatic Cancer after Resection and During Adjuvant Chemotherapy

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ABSTRACT

Background/Aim: Adjuvant chemotherapy for 6 months is the current standard of care after potentially curative resection of pancreatic cancer and yields an overall survival of 15–20 months. Early tumor recurrence before or during adjuvant chemotherapy has not been evaluated so far. These patients may not benefit from adjuvant treatment. **Patients and Methods:** Thirty-five patients with resection of ductal pancreatic carcinoma and adjuvant chemotherapy with gemcitabine were analyzed between 2005 and 2007. All patients had a computed tomography (CT) scan before and during adjuvant chemotherapy after 2–3 months, 12/35 patients had a histologically confirmed R1 resection. Recurrence of pancreatic cancer was determined by CT scan and the clinical course. **Results:** Median survival of 35 patients with resected pancreatic cancer was 19.7 months, and the 2-year survival was 44%. Thirteen (37%) of the 35 patients analyzed with a CT scan showed tumor recurrence during adjuvant chemotherapy. Overall survival of patients with tumor recurrence was 9.3 months with a 2-year survival rate of 13%, whereas median overall survival of patients without early relapse was 26.3 months (P<0.001). Local recurrence of pancreatic cancer occurred in 38% (5/13); 46% (6/13) of patients developed distant metastasis, and 38% (5/13) developed lymph node metastasis. Early tumor recurrence during or adjuvant chemotherapy did not correlate with R status (R1 *vs* R0, P=0.69), whereas histologically confirmed lymph node invasion (pN0 *vs* pN1) and grading showed a statistically significant correlation with early relapse (P<0.05). **Conclusion:** A significant fraction of patients with resected pancreatic cancer have early relapse during adjuvant chemotherapy, especially those with lymph node metastasis. Radiologic examinations prior to and during adjuvant chemotherapy will help to identify patients with tumor recurrence who are unlikely to benefit from adjuvant treatment and will need individualized palliative chemotherapy.

Key Words: Adjuvant chemotherapy, pancreatic cancer, recurrence

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Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the Western world with a 1-year survival rate of approximately 19% and a 5-year survival rate of less than 5%.[1] Only 5%–25% of patients present with resectable pancreatic cancer, but even in patients with R0 resected tumours, 5-year survival is no more than 20% with a median survival between 12 and 20 months.[2-5] Randomized controlled Phase III trials have demonstrated that adjuvant chemotherapy with gemcitabine improves median disease-free survival of R0 as well as of R1 resected pancreatic adenocarcinoma from 5–7 months to 10–13 months.[3,6,7] Recent Phase III trials have confirmed a survival benefit for adjuvant chemotherapy with 5-fluorouracil that is comparable to gemcitabine.[5,8-10] Adjuvant chemotherapy is therefore the standard of care in Europe for resectable pancreatic cancer.[11,12] However, the majority of patients will die of pancreatic cancer after tumor resection within a year. Nevertheless, no data are available about the onset and proportion of patients with tumor recurrence during or before adjuvant therapy. Identification of patients who may benefit from early combination chemotherapy with gemcitabine,[13] eg, gemcitabine–erlotinib,[14] oxaliplatin-irinotecan-leucovorin-5-fluorouracil,[15] or second-line therapies,[16,17] will allow longer survival in selected individual patients, whereas best supportive care will prevent unnecessary toxicity in patients with poor performance status. The

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role of postoperative Ca19-9 level as a predictor for tumor recurrence has been well established[8] and will therefore not be examined in this work. The aim of this study is to determine the rate of tumor recurrence before or during adjuvant therapy and to identify risk factors that may predict early recurrence.

PATIENTS AND METHODS

Between January 2005 and December 2007, 35 patients with histologically proven adenocarcinoma of the pancreas underwent tumor resection with curative intent at the University Hospital Freiburg, Germany. All patients received adjuvant chemotherapy with gemcitabine (1000 mg/m^2 per week), according to the protocol of the CONKO-001 trial,[3] and had routine computed tomography (CT) scan before and every 2–3 months during adjuvant chemotherapy with gemcitabine. Tumor recurrence was determined by follow-up with a CT scan and the clinical course. In 2 cases, questionable lesions were histologically proven by needle biopsy. Statistical analysis of overall survival was performed using the Kaplan–Meier method using PASW Statistics for Windows (IBM SPSS Statistics, version 18.0).

RESULTS

The median postoperative overall survival of the 36 patients was 19.7 months and the 2-year survival rate was 44%. Thirteen of 35 patients (38%) displayed early tumor recurrence during (n=13) the time period of adjuvant chemotherapy (6 months), the median time to tumor recurrence was 3.7 months after initial resection. Median overall survival of the patients with early tumor recurrence was 9.3 months, which was significantly less than 26.3 months for the patients without early tumor recurrence [P<0.001, Figure 1]. The 2-year survival rate of patients with early tumor recurrence was 13%, as compared with 60% in patients without early recurrence. Early local tumor recurrence occurred in 38% (5/13) of patients, and distant metastasis in 46% (6/13) of patients. Early lymph node metastases were detected in 38% (5/13) of patients.

In order to determine potential factors that may predict early pancreatic cancer recurrence, the correlation of different features of the tumor with early recurrence was statistically analyzed using the Chi-square test. R0 *vs* R1 resections were not associated with early tumor recurrence (35% *vs* 42% early recurrence; P=0.69), whereas histologically confirmed lymph node metastasis (pN0 *vs* pN1) at initial tumour resection correlated (borderline) with early tumor recurrence (20% *vs* 50% early recurrence; P=0.07). In addition, tumor grading strongly correlated with early tumor recurrence (early recurrence in 7 out of 10 (70%) patients with G3 or G4 tumors *vs* 6 out of 25 (24%) patients with G1 or G2 tumors; P<0.02).

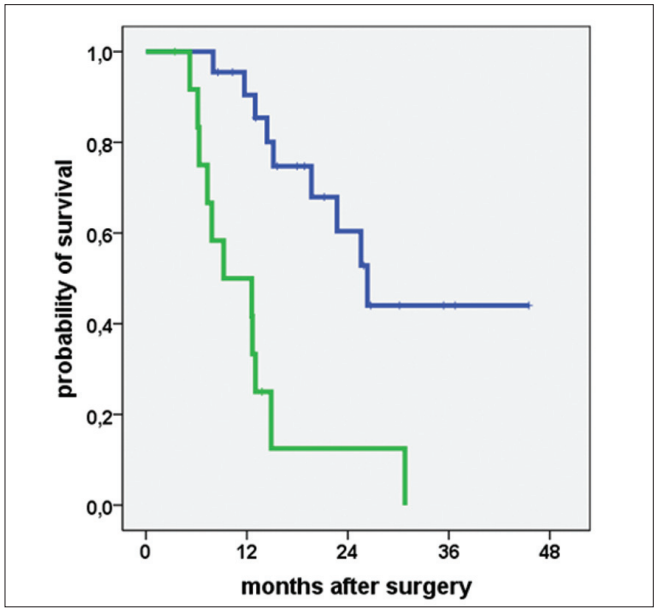

Figure 1: Kaplan–Meier curve of overall survival (n=35). Green: patients with early tumor recurrence during adjuvant chemotherapy, blue: no early tumour recurrence (median survival 9.3 months *vs* 26.3 months, $P \leq 0.001$)

DISCUSSION

The median disease-free survival following complete resection of pancreatic cancer and adjuvant chemotherapy with gemcitabine was reported as 13.4 months and 6.9 months for untreated patients.[3,18] The CONKO-001 trial demonstrated a longer disease-free survival with adjuvant chemotherapy in R0- and R1-resected patients,[3] and other studies confirmed the benefit of adjuvant chemotherapy.[10,19,20] We identified initial lymph node involvement and tumor grade as risk factors for early tumor recurrence, but not the resection status R0 *vs* R1. In general, overall survival remains poor due to tumor recurrence in almost all patients. European Society for Medical Oncology guidelines[21] as well as the national German Society for Digestive and Metabolic Diseases guidelines[11] lack any recommendation for systematic follow-up of patients during adjuvant therapy. Likewise, National Comprehensive Cancer Network (NCCN) guidelines suggest baseline CT scan before adjuvant treatment, but no imaging during chemotherapy.[22] This may be due to the lack of data evaluating the onset of tumor recurrence during adjuvant chemotherapy. In our population, 37% (13/35) patients had an early tumor recurrence during adjuvant chemotherapy that resulted in a significant shorter overall survival of 9.3 months as compared with 26.3 months in patients without early recurrence. Only very limited data are available on early tumor recurrence during adjuvant treatment, because existing trials on adjuvant therapy examined only general, clinical evident tumor recurrence, and did not analyze the onset of tumor

recurrence during adjuvant chemotherapy.[3,4,12,18] Recently, it was shown that postoperative Ca-19 levels, which were not routinely determined in our study, have a discriminatory value.[23] In the postoperative setting the authors stated that patients with a postoperative CA 19-9 level >180 U/mL have a worse survival than those with CA 19-9 lower than 180 U/mL. These patients should be considered for other therapeutic strategies.

Given the significantly longer overall survival of patients without early pancreatic cancer recurrence in our population, detection of early recurrence has important prognostic consequences. In addition, the therapeutic algorithm will change when patients develop metastasis or tumor recurrence during adjuvant therapy.[11,21,24] Tumor recurrence during adjuvant treatment with gemcitabine, 5-fluorouracil or chemoradiation demonstrates a lack of efficacy of the regimen used. Chemoradiation, second-line chemotherapy[16,17] or intensification of therapy, eg, combination therapies with gemcitabine/erlotinib, gemcitabine/capecitabine, or 5-FU/irinotecan/oxaliplatin[13,14,25,26] are able to prolong survival in selected patients, even though a survival benefit of an intensified survival strategy has not been demonstrated in randomized trials so far. On the other hand, patients with a poor performance status may be best served by best supportive care without any systemic treatment.[15,26] Identification of patients with early recurrence of pancreatic cancer is therefore an important issue, as regular staging of the tumor during chemotherapeutic treatment, eg, using CT scans, allows the selection of an appropriate regimen and avoids unnecessary cytotoxic treatment. Clinical practice guidelines should therefore include a recommendation for regular staging of patients during adjuvant treatment. Because the median time to early tumor recurrence was only 3.6 months in our study, we propose an initial postoperative CT scan, followed by regular staging every 2–3 months as recommended in the palliative setting[21] and by the current NCCN guidelines.

We identified initial lymph node involvement and tumor grade as risk factors for early tumor recurrence, but not the resection status R0 *vs* R1, even though R1 resection is known to be an important risk factor for overall survival.[12,21] In the near future there may be important molecular prognostic factors for the selection of appropriate chemotherapy regimens (eg, MMP7, RRM1, ERCC1), which will lead to better identification of patients for treatment than CT follow-up screening.[27-29]

In summary, especially patients with lymph node metastasis should receive regular response evaluation during adjuvant chemotherapy. At present, not only the patients with lymph node metastasis should receive regular response evaluation but all of the patients should have a baseline CT before any adjuvant treatment. These findings point to a potential benefit for patients undergoing resection of pancreatic cancer, even in those with extensive disease.

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